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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
PORTNER, V	
ART UNIT	PAPER NUMBER
1641	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/488,737	Applicant(s) Lissolo
	Examiner Portner	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Jan 20, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-16* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-16 are pending.

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

2. The disclosure is objected to because of the following informalities: on page 7, line 5 as SEQ ID NO is missing, it appears that the SEQ ID NO should be SEQ ID NO 1; on page 31, line 5 as SEQ ID NO is missing, it appears that the SEQ ID NO should be SEQ ID NO 2; on page 37, line 20, SEQ ID NO 1 is recited, it appears that this should be SEQ ID NO 2 .

Priority

3. If applicant desires priority under 35 U.S.C. 119 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now patent no." should follow the filing date of the parent application. If a parent

application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

4. The first sentence of the specification does not refer to the priority documents upon which Application is based; amendment of the specification to reflect the foreign priority entitled to this Application is requested.

Claim Objections

5. Claim 16 is objected to under 37 CAR 1.75© as being in improper form because a multiple dependent claim must depend upon other claims in the alternative and it depends upon both claim 1 and claim 10. See MPEP § 608.01(n). Accordingly, the claim 16 is not been further treated on the merits.

Claim Rejections - 35 U.S.C. § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 7, 9, 11, 13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the disclosed proteins of Helicobacter pylori and

immunogenic fragments therefrom, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses several proteins which are substantially purified and is immunoreactive with an antisera raised thereto; the specification on page 7, lines 20-24 and page 8, lines 1-16 states that the protein may be mutated at one or more amino acids by deletion, addition or substitution, no sequences either amino acid or nucleic acid are disclosed other than the N-terminal sequence of the 50 kDa antigen but this sequence does not define the active cite(s) of the 50 kDa protein or any of the other mutated proteins claimed. No specific changes which will not effect the over structure and function of the protein are described. No specific guidance directing to where changes could be tolerated and still maintain the desired activity is not disclosed. The claimed fragments and/or mutated protein need only be capable of reacting with an antisera, therefore claims encompass the deletion, substitution or insertion of any combination thereof, therefore **any** amino acid is being claimed, and **no** specific location for where the deletion, substitution or insertion or any combination thereof within the mutated protein or fragment is recited, if all the amino acids are deleted or substituted or inserted the resulting synthetic peptide could result in a peptide not taught and enabled by the specification. No pharmaceutical compositions

that comprise specific fragments that are able to treat or prevent Helicobacter infection are taught.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984",(pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes:

1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge;

2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix;

3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acid in a protein sequence to be changed to any other, as well as introducing deletions and insertions. The reference goes on to

teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The substitution of **any** amino acid in **any** location within the protein would not predictably result in a stable molecule. Specific amino acids in specific locations which result in stable mutations are not taught. The specification does not provide guidance on how any amino acid can be deleted, substituted or inserted or any combination thereof for the production a stable and active fragments with the functional characteristics of the native protein nor does the specification provide guidance on how any location can be used to produce a stable polypeptide. No working examples are shown containing the missing information. Without such information, one of skill in the art could not predict which deletions, substitutions or

insertions or any combination thereof would result in the desired product. Accordingly, one of skill in the art would be required to perform undue experimentation to use any amino acid at any location to produce a stable active protein. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation. In light of the fact that the mutant proteins of claims 7 and 9 are not so enabled that the person of skill in the art could make and use them, the claimed monospecific antibodies are also not enabled.

It would therefore require undue experimentation on the part of the skilled artisan to make polyclonal antibodies with the instantly claimed binding specificity to a protein or polypeptide that is not evidence original descriptive support which enables the production and isolation of monospecific antibodies to the mutant protein.

8. Claims 7-11, 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 7 recites the phrases: "by fragmentation and/or mutation" and "capable of being recognized by an antiserum raised against a protein". The phrase "a protein" lacks antecedent basis in claim 1. The size, nature or means of fragmentation are not clear; the claim as now written could be claiming a single amino acid of the original polypeptide which has been

fragmented. Therefore the recitation of the word "fragmentation" fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "capable of" has been held that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. In re Hutchison, 69, USPQ 138. This rejection could be obviated by amending the claim to recite --antigenic fragments-- or --immunogenic fragments-- or another phrase which is comparable to the suggested phrases above.

Claim 7: The phrase "and/or" does not clearly set forth the invention as it is not clear that the invention is a mutant fragment or a mutated protein or a fragment of the Helicobacter protein. Clarification is requested.

The type of mutation which still provides for antigenicity and recognition as an Helicobacter pylori protein is not clearly defined in the claims. Where or what type of mutation which would allow for alterations but still maintain the proteins antigenic nature is not clearly set forth, therefore the recitation of the word "mutation" fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. In claims 8-11, the phrase "a protein or a polypeptide lacks antecedent basis in claim from which they depend.

11. Claims 12 and 13 do not further limit the claim from which they depend and therefore does not distinctly claim Applicant's invention.

12.Claims 14-15 recite methods steps in the passive voice, this does not distinctly claim Applicant's invention. Amendment of the claim to recite positive steps could obviate this rejection.

Claim Rejections - 35 U.S.C. § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

14. Claims 1,4, 6, 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Landini et al (1989).

Landini et al disclose antigens which are reactive with substantially purified Helicobacter pylori antigens, wherein the approximate molecular weight of two the isolated proteins were 34 and 28 kD and was considered to be a Helicobacter pylori specific antigen which evidenced significantly higher IgG reaction with patient samples in comparison to other antigens identified.

(See abstract, and Figure 2, page 186); the 28 kDa protein reads on the now claimed 30 kDa and the 34 kDa reads on the antigen of 32-35 kDa, as the disclosed relative molecular weight value is within the acceptable range of variance when determining relative molecular weight by SDS-PAGE gel electrophoresis. Landini obtained the antigen by a materially different process but the isolated and purified protein of Landini appears to be the same or equivalent protein to the one now claimed and therefore anticipates the instantly claimed invention.

15. Claims 1-3,5-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Husson et al (1993).

Husson et al disclose antigens which substantially purified Helicobacter pylori antigens which are capable of reacting with antibodies, wherein the approximate molecular weight of the isolated proteins were 57, 54 (a heat shock protein and therefore not immunoreactive with catalase), 52,48,45,37,33,30 and 29 kDa (see page 2697, column 1, paragraph 2) . The disclosed antigens were Husson obtained by a materially different process but the isolated and purified protein of appear to be the same or equivalent proteins of 54, 50, 32-35 and 30 kDa now claimed and therefore anticipates the instantly claimed invention.

16. Claims 1,2, 3-4, 5, 6-8,9,15 are rejected under 35 U.S.C. 102(e) as being anticipated by Calenoff (US Pat.5,567,594, filing date: December 20, 1993).

Calenoff discloses antigens which are substantially purified Helicobacter pylori antigens reactive with antibodies, wherein the approximate molecular weight of the isolated proteins were:(See columns 13-16)

53 kDa(designated2.7.3)

51 kDa (designated 5.12.1), 49 kDa (designated 2.12.1), 48 kDa(designated 1.12.1)

34 kD (designated:2.12.1 and 3.12.3), 36 kDa(designated 8.12.2) and

31 kDa(designated 3.12.4 and 4.12.3), 29 kDa (designated 3.12.5).

The disclosed protein antigens read on the now claimed protein antigens of 54, 50, 32-35 and 30 kDa as the values are within the acceptable range of variance when determining relative molecular weight by SDS-PAGE gel electrophoresis and teaches the evaluation of the antigens to define epitope fragments of the antigens that are immunoreactive with patient antibodies (col. 18, lines 48-55). Antibodies specific for bacterial antigens are taught for the purification of antigens which contain epitopes immunologically identifiable with epitopes of Helicobacter pylori (see col. 19, lines 66-67 and col. 20, liens 1-11). Calenoff obtained the antigens by a materially different process but the isolated and purified protein of Calenoff appears to be the same or equivalent protein to the one now claimed and teaches means and methods for the attainment of purified proteins. Therefore, Calenoff anticipates the instantly claimed invention.

17. Claims 1,2,7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al (1991).

Dunn et al disclose a Helicobacter pylori antigen of 54 kDa, wherein the antigenic protein shared greater than 50% homology with the amino terminal of 33 residues of to other bacterial heat shock proteins. Therefore, the reference disclose mutant proteins of Helicobacter pylori 54 kDa antigen. The disclosure anticipates the now claimed proteins with a relative molecular weight of about 54 kDa.

18. Claims 1,2,7-9,15 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrero et al (1995).

Ferrero et al disclose a Helicobacter pylori antigen of 54 kDa, wherein the antigenic protein shared homology with E.coli bacterial heat shock protein and designated as hspB. Therefore, the reference disclose mutant proteins of Helicobacter pylori 54 kDa antigen. The disclosure anticipates the now claimed proteins with a relative molecular weight of about 54 kDa.

19. Claims 1-5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Geis et al (1993).

Geis et al disclose a Helicobacter pylori antigens of 53,51, 49, 29.5 kDa. The reference discloses the now claimed proteins with a relative molecular weight of about 54, 50 and 30 kDa

as the values are within the acceptable range of variance when determining relative molecular weight by SDS-PAGE gel electrophoresis. The 50 kDa antigen of the prior art would inherently comprise recited SEQ ID No 1. The disclosure anticipates the now claimed invention

20. Claims 1,2, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Leying et al (1992).

Leying et al disclose a Helicobacter pylori antigen of about 54 kDa, wherein the 54 kDa antigenic protein was determined to be a flagellin antigen. The presence of Helicobacter 54 kDa antigen was determined through immunoreaction with antigen specific antibodies (see page2872, col. 2, paragraph 4). Therefore, the reference anticipates the now claimed proteins with a relative molecular weight of about 54 kDa and 30 kDa (see page 405, Table 2, top of page)..

21. Claims 1,5,8,10-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bolin et al (1995).

Bolin et al show a monospecific, monoclonal antibody used in a method of diagnosis of Helicobacter in a biological sample, wherein the monoclonal antibody specifically reacted with an outer membrane antigen of 30 kDa. The monoclonal antibody was used as a composition which anticipates the now claimed pharmaceutical compositions as the recited intended use of a composition does not define over the prior art. The monoclonal antibody need not specifically

bind to the mutated region of the polypeptide but must only recognize specifically bind to the protein of claim 1. The disclosure of the reference anticipates the now claimed invention.

22. Claims 1,3-5, 7, 8, 10-11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Doig et al (1994).

Doig et al disclose membrane proteins of 31, 48, 50 and 51 kDa which would not be immunoreactive with catalase antibodies, wherein the antigens were determined to have other antigenic characteristics, wherein the values are within the acceptable range of variance when determining relative molecular weight by SDS-PAGE gel electrophoresis and read on the now claimed antigens of 30, 50 kDa. Inherently the 50 kDa protein would evidence the N-terminal amino acid claimed (claim 4). The antigens were used as pharmaceutical composition to stimulate an immune response in a mammalian host for the production of monospecific, monoclonal antibodies (see material and methods section and Table 1, page 4528). The reference anticipates the now claimed invention.

23. Claims 1,2, 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Yokota et al (1994).

Yokota et al disclose a Helicobacter pylori antigens of 54 and 30 kDa, wherein the 54 kDa antigenic protein was determined to be a heat shock protein. Therefore, the reference anticipates the now claimed proteins with a relative molecular weight of about 54 kDa and 30 kDa (see page 405, Table 2, top of page).

24. Claims 1-2,5-6, 8,10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Alemohammad (US Pat.5,262,156).

Alemohammad discloses an antigenic composition comprising substantially purified Helicobacter pylori antigens reactive with antibodies, wherein the approximate molecular weight of the isolated proteins were 31 kDa, 33 kDa (see column 2, Table 1 and col. 5, lines 1-23), as well as a 54 kDa antigen defined as a putative flagellin antigen(col. 2, line 36). The 54 kDa antigen would not immunoreact with catalase antibodies as it would have different immunoreactive epitopes. Alemohammad teaches the affinity purification of antibodies to using Helicobacter antigen on the solid phrase (column 7,lines 40-55) in order to obtain monospecific antibodies. These antibodies in turn were used as a control for a diagnostic method. Alemohammad obtained the antigens by a materially different process but the isolated and purified protein of Alemohammad appears to be the same or equivalent protein to the one now claimed and therefore anticipates the instantly claimed invention.

25. Claims 1, 6 and 10,12, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Mizuta et al (1993, abstract).

Mizuta et al disclose monoclonal antibodies which are reactive and recognize Helicobacter pylori antigens, wherein one of the antigens is 33-35 kDa. The reference discloses an immunoblotting diagnostic method which demonstrated 7 major protein antigens which reacted with hyper immune sera. A monoclonal antibody immunoreactive with the 33-35 kDa

antigen is disclosed. Mizuta et al obtained the antigens by a materially different process but the isolated and purified protein of Mizuta et al appears to be the same or equivalent protein to the one now claimed and therefore anticipates the instantly claimed invention.

26. Claims 1,5 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen et al (1995).

Andersen et al disclose the isolation and purification of diagnostic low molecular weight Helicobacter pylori antigens, wherein one of the disclosed antigens is 30 kDa. Inherently this antigen is the same or equivalent antigen as now claimed because the source and mode of isolation were the same. The reference anticipates the now claimed invention.

27. Claims 1,3-4,8 are rejected under 35 U.S.C. 102(b) as being anticipated by Exner et al (1995).

Exner et al disclose the isolation and purification of Helicobacter pylori antigens of apparent molecular weights of 48, 49, 50 and 67 kDa. Inherently these antigens the same or equivalent antigen to the now claimed 50 kDa antigen. The reference anticipates the now claimed invention

28. Claims 1-6,8 are rejected under 35 U.S.C. 102(e) as being anticipated by Pronovost et al (US Pat. 5,814,455 and 5,846,751).

Pronovost et al disclose Helicobacter pylori antigens of 29 kDa, 31 kDa, 45 kDa, 52 kDa, 56 kDa (see all claims). Inherently the antigens disclosed correspond to, are the same as or equivalent to the claimed antigens of about 30 kDa, 32 kDa, 50 kDa and 54 kDa because the relative molecular weights of the antigens in the prior art are within the acceptable range of variance when the molecular weight is determined by SDS-PAGE. The N-terminal sequence of the about 50 kDa antigen would be an inherent characteristic of the disclosed antigens of the prior art. The reference anticipates the now claimed invention.

29. Claims 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Cordle et al (US Pat. 5,260,057).

Cordle et al disclose pharmaceutical compositions that comprise isolated and concentrated specific immunoglobulins for Helicobacter pylori surface membrane antigens. The reference anticipates the now claimed compositions which recite open language and permit the presence of other antibodies to other Helicobacter pylori antigens as the antibody compositions were raised to whole cell antigen compositions which would comprise all of the antigens present in Helicobacter pylori.

30. Claims 10-13, 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ruiz et al (WO94/06474).

Ruiz et al disclose pharmaceutical compositions that comprise isolated and concentrated specific immunoglobulins for Helicobacter pylori urease antigen, one of the subunits being of about 30 kDa, and the use of the antibodies in detecting Helicobacter infection. The reference anticipates the now claimed compositions which recite open language and permit the presence of other antibodies to other Helicobacter pylori antigens.

Conclusion

31. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

32. Thomas et al is cited to show a composition that is immunogenic but not protective against infection (1993).

33.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be changing February 7, 1998. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1641.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.
VGP
May 24,2000

James C. Housel
JAMES C. HOUSEL 6/5/00
SUPERVISORY PATENT EXAMINER